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PATENT

REMARKS

The foregoing amendments are made to insert the Sequence ID Numbers into the specification. No new matter has been added.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "Version with markings to show changes made."

Respectfully submitted,

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Version with markings to show changes made

In the Specification:

Paragraph beginning on page 9, line 34, has been amended as follows:

Exemplary hinge sequences may be, but are not limited to: N-S; Q-A; N-S-G-S-P (SEQ ID NO:1); A-A-S-T-P (SEQ ID NO:2); N-S-G-P-T-P-P-S-P-G-S-P (SEQ ID NO:3); S-S-P-G-A (SEQ ID NO:4); and the like. It is contemplated that such hinge sequences may be employed as repeat units to increase further the separation between the fused polypeptides.

Paragraph beginning on page 16, line 29, has been amended as follows:

To prepare the fused gene having the hSOD coding sequence at the 3'-terminus in the direction of transcription separated from the proinsulin gene by a "spacer" of codons coding for K-R-S-T-S-T-S (SEQ ID NO:5), the following fragments were ligated. A 671bp BamHI-Sall fragment containing the GAP promoter, the proinsulin gene and codons for the spacer amino acids; a 14bp Sall-NcoI synthetic adapter, which codes for the last spacer amino acids as a junction of both genes; and a 1.5kb NcoI-BamHI fragment isolated from pC1/1 GAPSOD described in copending application 609,412 (supra), which includes the hSOD coding region, 56bp of hSOD terminator and 934bp of GAP terminator region. The resulting cloned fragment was isolated and inserted into BamHI digested, alkaline phosphatase treated pC1/1.

Paragraph beginning on page 17, line 11, has been amended as follows:

Plasmids homologous to pYSI1 and pYSI2, but using the yeast pyruvate kinase (PYK) gene instead of hSOD gene, were also constructed. pPKI1 contains the PYK coding

sequence fused to the amino-terminus of the human proinsulin gene under regulation of the yeast PYK promoter and yeast GAP terminator. pPKI2 contains the PYK coding sequence of the 3'-terminus in the direction of transcription separated from the proinsulin gene by a "spacer" of codons coding for K-R-S-T-S (SEQ ID NO:6). This fused gene is under regulation of the GAP promoter and PYK terminator.

Paragraph beginning on page 26, line 25, has been amended as follows:

ARV-300 5' AATTCAGGTGTTGGAGC (SEQ ID NO:7)
GTCCACAACCTCGGTAC 5' ARV-301 (SEQ ID NO:8)

Paragraph beginning on page 28, line 12, has been amended as follows:

5'-TTAAAATCACTTGCCATGGCTCTCCAATTACTG (SEQ ID NO:9)

Paragraph beginning on page 29, line 14, has been amended as follows:

5'-GGTGTTTTACTAAAGAATTCCGTCGACTAATCCTCATCC.
(SEQ ID NO:10)

Paragraph beginning on page 32, line 18, has been amended as follows:

A second BamHI (460 bp) fragment coding for amino acid residue 41 to 201 of IGF-2 and for the α -factor terminator (see EPO 123 228) was ligated to the following linker:

EcoRI

Sall

AATTCATGGCTTACAGACCATCCGAAACCTTGTGTGGTGGTGAATTGG

GGTACCGAATGTCTGGTAGGCTTTGGAACACACCACCACTTAACCAGCT

(SEQ ID NO:11)

The linker provides for an EcoRI overhang, an ATG codon for methionine and for codons 1-40 of IGF2 and Sall overhang.